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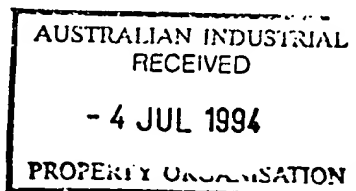
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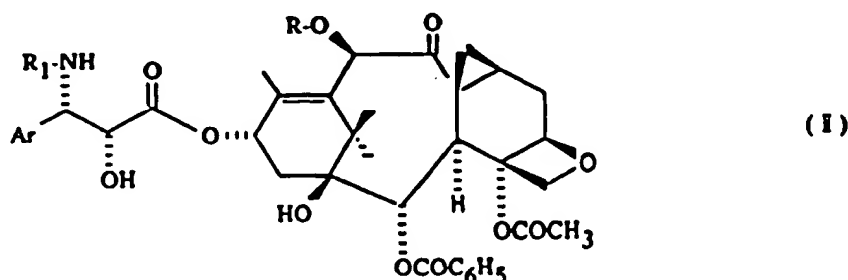
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(54) Title: NOVEL TAXOIDS, PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(54) Titre: NOUVEAUX TAXOIDES, LEUR PREPARATION ET LES COMPOSITIONS PHARMACEUTIQUES QUI LES CONTIENNENT



(57) Abstract

Novel taxoids of general formula (I), the preparation thereof and pharmaceutical compositions containing same. In general formula (I), Ar is an aryl radical; R is a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical; R₁ is a benzoyl radical or a radical of formula R₂-O-CO- wherein R₂ is an optionally substituted alkyl radical, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclyl. The novel products of general formula (I) have remarkable antitumour activity.

(57) Abrégé

Nouveaux taxoïdes de formule générale (I), leur préparation et les compositions pharmaceutiques qui les contiennent. Dans la formule générale (I), Ar représente un radical aryle, R représente un atome d'hydrogène ou un radical acétyle, alcoyloxyacétyle ou alcoyle, R₁ représente un radical benzoyle ou un radical de formule R₂-O-CO- dans lequel R₂ représente un radical alcoyle éventuellement substitué, alcényle, alcynyle, cycloalcoyle, cycloalcényle, bicycloalcoyle, phényle, hétérocyclyle. Les nouveaux produits de formule générale (I) présentent une activité antitumorale remarquable.

VERIFIED TRANSLATION OF PCT 56531/94

IN THE MATTER OF an Australian
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PCT Application PCT/FR93/01201

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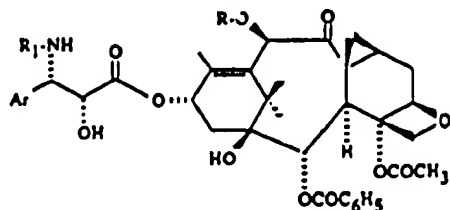
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| <p>(71) Applicant: RHONE-POULENC RORER S.A. [FR/FR]; 20, avenue Raymond-Aron, F-92160 Antony (FR).</p> <p>(72) Inventors: Hervé BOUCHARD; 114, avenue Danielle-Casanova, F-94200 Ivry-sur-Seine (FR). Jean-Dominique BOURZAT; 36, boulevard de la Libération, F-94300 Vincennes (FR). Alain COMMERÇON; 1 bis, rue Charles-Floquet, F-94400 Vitry-sur-Seine (FR).</p> <p>(74) Representative: Jacques PILARD; Rhône-Poulenc Rorer S.A., Patents Directorate, 20, avenue Raymond-Aron, F-92165 Antony Cédex (FR).</p> | | <p>Published With the International Search Report. With modified claims.</p> |

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(8)

(87) A butterfly

Novel isoxazoles of general formula (I), the preparation thereof and pharmaceutical compositions containing same. In general formula (I), Ar is an aryl radical; R is a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical; R₁ is a benzoyl radical or a radical of formula R₂-O-CO- wherein R₂ is an optionally substituted alkyl radical, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclyl. The novel products of general formula (I) have remarkable antitumor activity.

(57) Abbriv.

Nouveaux tioxides de formule générale (7), leur préparation et les compositions pharmaceutiques qui les contiennent. Dans la formule générale (7), R représente un radical aryle, R' représente un atome d'hydrogène ou un radical acétyle, alcoyloxyéthyle ou alcoyle, K₁ représente un radical benzoyloxy ou un radical de formule R₁-O-CO- dans lequel R₁ représente un radical alcoyle éventuellement substitué, alkoyle, alkoylexy, cycloalkoxy, cycloalkyle, bicycloalkoxy, phényle, tétracycyle. Les nouveaux produits de formule générale (1) présentent une activité antitumorale remarquable.

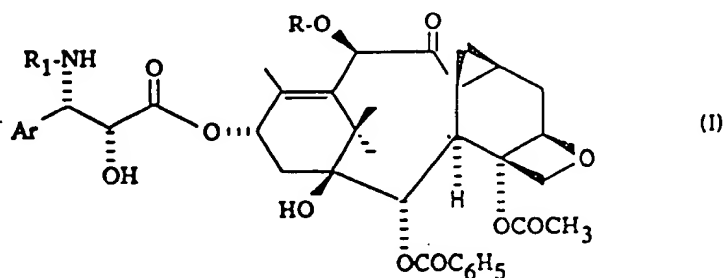
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NEW TAXOIDS, THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to new taxoids
of general formula:



- 5 their preparation and pharmaceutical compositions
containing them.

In general formula (I),

Ar represents an aryl radical,

- R represents a hydrogen atom or an acetyl, alkoxyacetyl
10 or alkyl radical,

R₁ represents a benzoyl radical or a radical R₂-O-CO- in
which R₂ represents:

- a straight or branched alkyl radical
containing 1 to 8 carbon atoms, an alkenyl radical
15 containing 2 to 8 carbon atoms, an alkynyl radical
containing 3 to 8 carbon atoms, a cycloalkyl radical
containing 3 to 6 carbon atoms, a cycloalkenyl radical
containing 4 to 6 carbon atoms or a bicycloalkyl
radical containing 7 to 11 carbon atoms, these radicals
20 being optionally substituted by one or more
substituents chosen from halogen atoms and hydroxy

radicals, alkyloxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals
5 (optionally substituted at position 4 by an alkyl radical containing 1 to 4 carbon atoms or by a phenylalkyl radical whose alkyl portion contains 1 to 4 carbon atoms), cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6
10 carbon atoms, phenyl radicals, cyano radicals, carboxy radicals or alkyloxycarbonyl radicals whose alkyl portion contains 1 to 4 carbon atoms,

- or a phenyl radical optionally substituted by one or more atoms or radicals chosen from halogen
15 atoms and alkyl radicals containing 1 to 4 carbon atoms or alkyloxy radicals containing 1 to 4 carbon atoms,

- or a saturated or unsaturated 4- to 6-membered nitrogen-containing heterocyclyl radical optionally substituted by one or more alkyl radicals
20 containing 1 to 4 carbon atoms,
it being understood that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals may be optionally substituted by one or more alkyl radicals containing 1 to 4 carbon atoms.

25 Preferably, Ar represents a phenyl or α - or β -naphthyl radical optionally substituted by one or more atoms or radicals chosen from halogen atoms (fluorine, chlorine, bromine, or iodine) and alkyl,

alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxy, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, it being understood that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α - or β -naphthyl radicals or alternatively Ar represents a 5-membered aromatic heterocyclic radical containing one or more atoms, which are identical or different, chosen from nitrogen, oxygen or sulphur atoms, optionally substituted by one or more substituents, which are identical or different, chosen from halogen atoms (fluorine, chlorine, bromine or iodine) and alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl

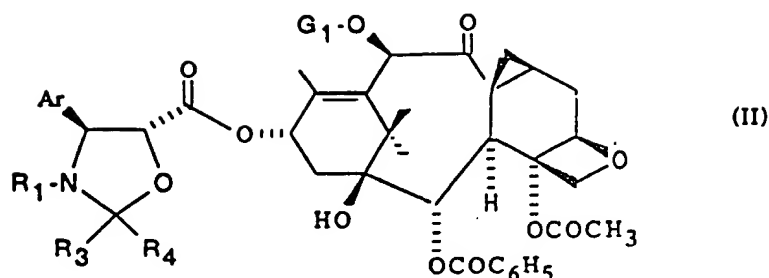
portion contains 6 to 10 carbon atoms, cyano radicals, carboxy radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each
5 alkyl portion contains 1 to 4 carbon atoms or alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

More particularly, Ar represents a phenyl, 2- or 3-thienyl or 2- or 3-furyl radical optionally
10 substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl, alkoxy, amino, alkylamino, dialkylamino, acylamino, alkoxycarbonylamino and trifluoromethyl radicals.

15 Still more particularly, Ar represents a phenyl radical optionally substituted by a chlorine or fluorine atom or by an alkyl (methyl), alkoxy (methoxy), dialkylamino (diethylamino), acylamino (acetylamino) or alkoxycarbonylamino (tert-
20 butoxycarbonylamino) or 2- or 3-thienyl or 2- or 3-furyl radical.

Of even more special interest are the products of general formula (I) in which Ar represents a phenyl radical and R_1 represents a benzoyl or
25 tert-butoxycarbonyl radical.

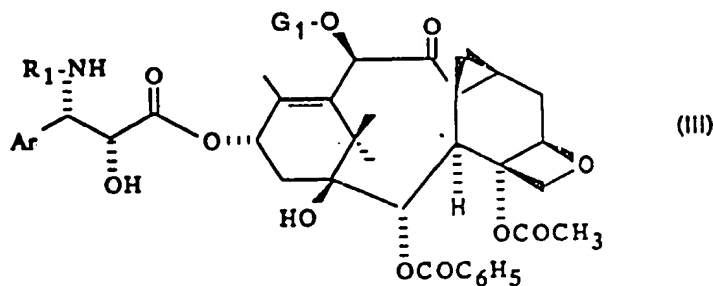
According to the present invention, the new taxoids of general formula (I) can be obtained from a product of general formula:



in which Ar and R₁ are defined as above and R₃ and R₄, which are identical or different represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical whose alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted by one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted by one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively R₃ represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted by a trihalomethyl radical such as trichloromethyl and R₄ represents a hydrogen atom, or alternatively R₃ and R₄ form, together with the carbon atom to which they are attached, a 4- to 7-membered ring, and G₁ represents a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical or a hydroxy-protecting group, the procedure being carried out, according to the meanings of R₃ and R₄, in the following manner:

1) when R₃ represents a hydrogen atom or an

alkoxy radical containing 1 to 4 carbon atoms or an optionally substituted aryl radical and P_4 represents a hydrogen atom, the product of general formula (II) is treated in acidic medium in order to obtain a product of general formula:



in which Ar , R_1 and G_1 are defined as above, whose G_1 radical is, if necessary, replaced by a hydrogen atom.

The deprotection of the side chain of the product of general formula (II) can also be carried out in the presence of an inorganic acid (hydrochloric acid or sulphuric acid) or an organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid or p-toluenesulphonic acid), used alone or in the form of a mixture, the procedure being carried out in an organic solvent chosen from alcohols (methanol, ethanol or isopropanol), ethers (tetrahydrofuran, diisopropyl ether or methyl t-butyl ether), esters (ethyl acetate, isopropyl acetate or n-butyl acetate), aliphatic hydrocarbons (pentane, hexane or heptane), halogenated aliphatic hydrocarbons (dichloromethane or 1,2-dichloroethane), aromatic hydrocarbons (benzene, toluene or xylenes) and nitriles (acetonitrile) at a

temperature of between -10 and 60°C, preferably between 15 and 30°C. The acid may be used in a catalytic or stoichiometric quantity or in excess.

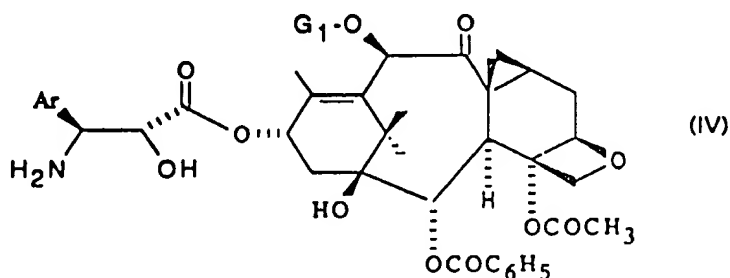
The deprotection can also be carried out under oxidizing conditions, using for example ammonium cerium(IV) nitrate in an acetonitrile-water mixture or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in water.

The deprotection can also be carried out under reducing conditions, for example by hydrogenolysis in the presence of a catalyst.

When G_1 represents a protecting group, it is preferably a 2,2,2-trichloroethoxycarbonyl or 2-(2-trichloromethylpropoxy)carbonyl radical whose replacement by a hydrogen atom is carried out using zinc, optionally combined with copper, in the presence of acetic acid, at a temperature of between 20 and 60°C or by means of an inorganic or organic acid such as hydrochloric acid or acetic acid in a solution in an aliphatic alcohol containing 1 to 3 carbon atoms or in an aliphatic ester such as ethyl acetate, isopropyl acetate or n-butyl acetate in the presence of zinc optionally combined with copper, or alternatively, when G_1 represents an alkoxycarbonyl radical, its optional replacement by a hydrogen atom is carried out by treatment in alkaline medium or by the action of a zinc halide under conditions which do not affect the rest of the molecule. Generally, the alkaline treatment is carried out by the action of ammonia in aqueous-

alcoholic medium, at a temperature close to 20°C. Generally, the treatment with a zinc halide, preferably zinc iodide is carried out in methanol at a temperature close to 20°C.

5 2) when R_3 and R_4 , which are identical or different, represent an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical whose alkyl portion contains 1 to 4 carbon atoms and the aryl portion is preferably an optionally substituted phenyl radical, or
 10 alternatively R_3 represents a trihalomethyl radical or a phenyl radical substituted by a trihalomethyl radical and R_4 represents a hydrogen atom, or alternatively R_3 and R_4 form, together with the carbon atom to which they are attached, a 4- to 7-membered ring, the product
 15 of general formula (II) is converted to the product of general formula:



in which Ar and G_1 are defined as above, which is acylated by means of benzoyl chloride or a reactive derivative of general formula:



in which R_2 is defined as above and X represents a halogen atom (fluorine or chlorine) or a residue $-O-R_2$

or $-O-CO-O-R_2$, to give a product of general formula (III) in which Ar, R_1 and G_1 are defined as above, whose G_1 radical is, if necessary, replaced by a hydrogen atom.

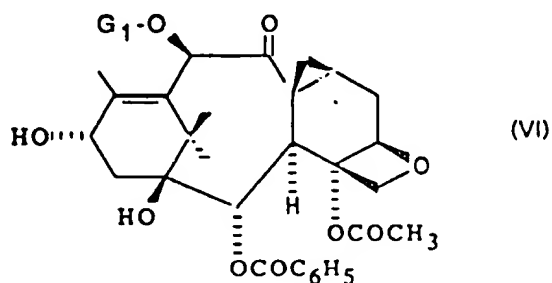
5 The products of general formula (IV) can be obtained by treating a product of general formula (II), in which Ar, R_1 and G_1 are defined as above, R_3 and R_4 , which are identical or different, represent an alkyl, aralkyl or aryl radical, or alternatively R_3 and R_4 form
10 together with the carbon atom to which they are attached a 4- to 7-membered ring, with an inorganic acid (hydrochloric acid or sulphuric acid) or an organic acid (formic acid) optionally in an alcohol containing 1 to 3 carbon atoms (methanol, ethanol or
15 isopropanol) at a temperature of between 0 and 50°C. Preferably, formic acid is used at a temperature close to 20°C.

 The acylation of the product of general formula (IV) by means of benzoyl chloride or a reactive
20 derivative of general formula (V) is carried out in an inert organic solvent chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane in the presence
25 of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is carried out at a temperature of between 0 and 50°C, preferably close to 20°C.

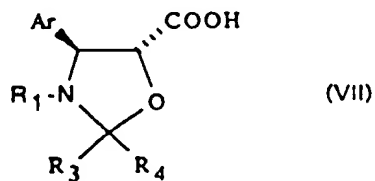
When the radical G_1 represents a protecting group, its replacement by a hydrogen atom is carried out under the conditions described above.

The products of general formula (II) can be obtained according to one of the following methods:

1) by esterification of the product of general formula:



in which G_1 is defined as above, by means of an acid of general formula:



in which Ar , R_1 , R_3 and R_4 are defined as above, or of a derivative of this acid.

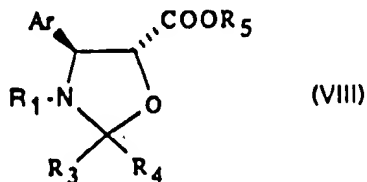
The esterification by means of an acid of general formula (VII) can be carried out in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridine) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons or aromatic hydrocarbons) at a temperature

of between -10 and 90°C.

The esterification may also be performed using the acid of general formula (VII) in anhydride form, the procedure being carried out in the presence of an activating agent (aminopyridine) in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons or aromatic hydrocarbons) at a temperature of between 0 and 90°C.

The esterification can also be performed using the acid of general formula (VII) in halide form or in anhydride form with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), the procedure being carried out in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons or aromatic hydrocarbons) at a temperature of between 0 and 80°C.

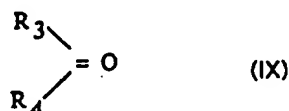
The acid of general formula (VII) can be obtained by saponification of an ester of general formula:



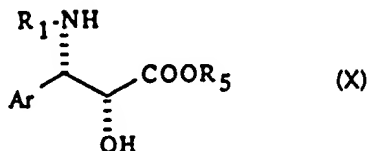
in which Ar, R₁, R₃ and R₄ are defined as above and R₅ represents an alkyl radical containing 1 to 4 carbon atoms optionally substituted by a phenyl radical.

Generally, the saponification is carried out by means of an inorganic base (alkali metal hydroxide, carbonate or bicarbonate) in aqueous-alcoholic medium (methanol-water) at a temperature of between 10 and 40°C.

The ester of general formula (VIII) can be obtained by the action of a product of general formula:

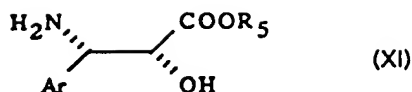


in which R_3 and R_4 are defined as above in the form of a dialkylacetal or an enol alkyl ether, on an ester of general formula:



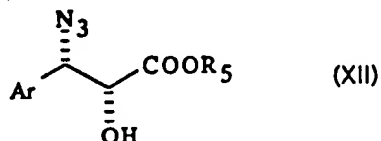
in which Ar , R_1 and R_5 are defined as above, the procedure being carried out in an inert organic solvent (aromatic hydrocarbon) in the presence of a strong inorganic acid (sulphuric acid) or organic acid (p-toluenesulphonic acid optionally in the form of a pyridinium salt) at a temperature of between 0°C and the boiling temperature of the reaction mixture.

The ester of general formula (X) can be obtained by the action of a product of general formula (V) on an ester of general formula:



in which Ar and R₅ are defined as above, the procedure being carried out in an organic solvent (ester, halogenated aliphatic hydrocarbon) in the presence of an inorganic or organic base at a temperature of
 5 between 0 and 50°C.

The product of general formula (XI) can be obtained by reduction of an azide of general formula:



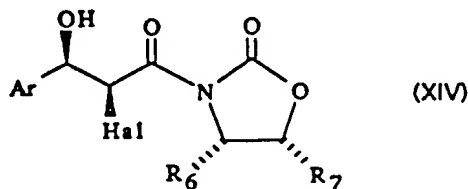
in which Ar and R₅ are defined as above, by means of hydrogen in the presence of a catalyst such as
 10 palladium on carbon, the procedure being carried out in an organic solvent (ester).

The product of general formula (XII) can be obtained by the action of an azide such as trimethylsilyl azide in the presence of zinc chloride
 15 or an alkali metal (sodium, potassium or lithium) azide in aqueous-organic medium (water-tetrahydrofuran) at a temperature of between 20°C and the boiling temperature of the reaction mixture, on an epoxide of general formula:



in which Ar and R₅ are defined as above, optionally prepared in situ.

The epoxide of general formula (XIII) can be obtained, optionally in situ, by dehydrohalogenation of
5 a product of general formula:



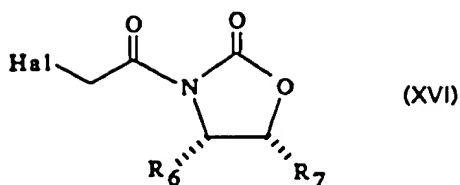
in which Ar is defined as above, Hal represents a halogen atom, preferably a bromine atom, and R₆ and R₇, which are identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms
10 or a phenyl radical, at least one being an alkyl radical or a phenyl radical, by means of an alkali-metal alcoholate, optionally prepared in situ, in an inert organic solvent such as tetrahydrofuran at a temperature of between -80°C and 25°C.

15 The product of general formula (XIV) can be obtained by the action of an aldehyde of general formula:



in which Ar is defined as above, on a halide of general
20 formula:

15

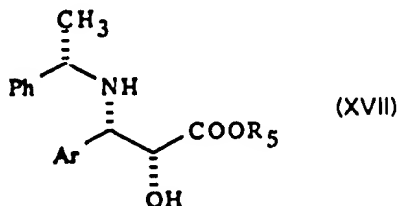


in which Hal, R_6 and R_7 are defined as above, anionized beforehand.

Generally, the procedure is carried out in an inert organic solvent chosen from ethers (ethyl ether) and halogenated aliphatic hydrocarbons (methylene chloride) at a temperature of between -80 and 25°C , in the presence of a tertiary amine (triethylamine) and an enolysing agent (di-n-butylboron triflate).

The product of general formula (XVI) can be obtained by the action of a halide of a haloacetic acid, preferably bromoacetic acid bromide, on the corresponding oxazolidinone.

The product of general formula (XI) can be obtained by hydrogenolysis of a product of general formula:



in which Ar and R_5 are defined as above and Ph represents an optionally substituted phenyl radical.

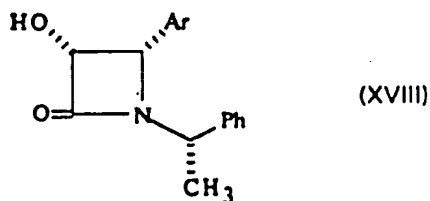
Generally, the hydrogenolysis is carried out

by means of hydrogen in the presence of a catalyst.
 More particularly, palladium on carbon containing 1 to
 10 % by weight of palladium or palladium dihydroxide
 containing 20 % by weight of palladium is used as
 5 catalyst.

The hydrogenolysis is carried out in an
 organic solvent or in a mixture of organic solvents. It
 is advantageous to carry out the procedure in acetic
 acid optionally combined with an aliphatic alcohol
 10 containing 1 to 4 carbon atoms such as a mixture of
 acetic acid-methanol at a temperature of between 20 and
 80°C.

The hydrogen necessary for the hydrogenolysis
 can also be provided by a compound which liberates
 15 hydrogen by chemical reaction or by thermal
 decomposition (ammonium formate). It is advantageous to
 carry out the procedure at a hydrogen pressure of
 between 1 and 50 bar.

The product of general formula (XVII) can be
 20 obtained by hydrolysis or alcoholysis of a product of
 general formula:



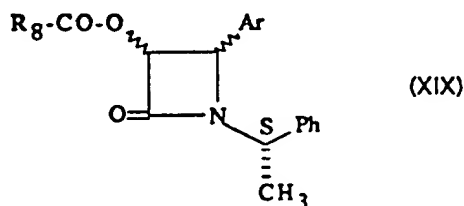
in which Ar and Ph are defined as above.

It is particularly advantageous to carry out

an alcoholysis by means of an alcohol of formula R_5-OH in which R_5 is defined as above, the procedure being carried out in acidic medium.

5 Preferably, the alcoholysis is carried out by means of methanol in the presence of a strong inorganic acid such as hydrochloric acid at a temperature close to the reflux temperature of the reaction mixture.

The product of general formula (XVIII) can be obtained by saponification of an ester of general
10 formula:

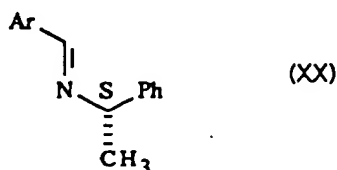


in which Ar and Ph are defined as above and R_8 represents an alkyl, phenylalkyl or phenyl radical, followed by separation of the 3R, 4S diastereoisomer of general formula (XVII) from the other diastereoisomers.

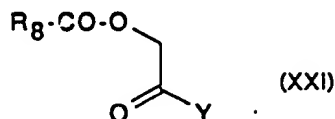
15 Generally, the saponification is carried out by means of an inorganic or organic base such as ammonium hydroxide, lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as a methanol-water or tetrahydrofuran-water mixture at a
20 temperature of between $-10^{\circ}C$ and $20^{\circ}C$.

The separation of the 3R,4S diastereoisomer can be carried out by selective crystallization from a suitable organic solvent such as ethyl acetate.

The product of general formula (XIX) can be obtained by cycloaddition of an imine of general formula:



in which Ar and Ph are defined as above, onto an acid
5 halide of general formula:



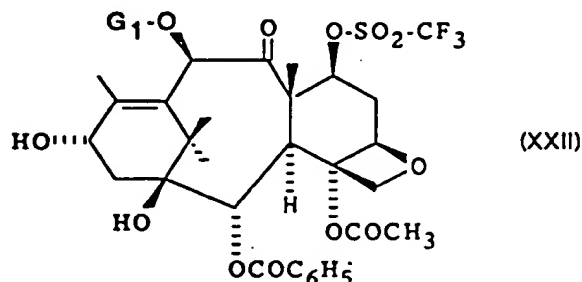
in which R_8 is defined as above and Y represents a halogen atom such as a bromine or chlorine atom.

Generally, the reaction is carried out at a temperature of between 0 and 50°C in the presence of a
10 base chosen from aliphatic tertiary amines (triethylamine) or pyridine in an organic solvent chosen from optionally halogenated aliphatic hydrocarbons (methylene chloride or chloroform) and aromatic hydrocarbons (benzene, toluene or xylenes).

15 The product of general formula (XX) can be obtained under conditions analogous to those described by M. Furukawa et al., Chem. Pharm. Bull., 25 (1), 181-184 (1977).

20 The product of general formula (VI) can be obtained by the action of an alkali metal halide (sodium iodide or potassium fluoride) or an alkali

metal azide (sodium azide) or a quaternary ammonium salt or an alkali metal phosphate, on a baccatin III or 10-deacetylbaccatin III derivative of general formula:



in which G_1 is defined as above.

5 Generally, the reaction is carried out in an organic solvent chosen from ethers (tetrahydrofuran, diisopropyl ether, methyl t-butyl ether) and nitriles (acetonitrile), alone or in the form of a mixture, at a temperature of between 20°C and the boiling temperature
10 of the reaction mixture.

The product of formula (XXII) in which G_1 represents a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical can be obtained by the action of a trifluoromethanesulphonic acid derivative such as the
15 anhydride or N-phenyltrifluoromethanesulphonimide, on baccatin III or 10-deacetylbaccatin III, which can be extracted according to known methods from yew leaves (*Taxus baccata*), optionally followed by protection in position 10, it being understood that in order to
20 obtain a product of general formula (XXII) in which G_1 represents an alkoxyacetyl or alkyl radical, it is necessary to treat beforehand the 10-deacetylbaccatin

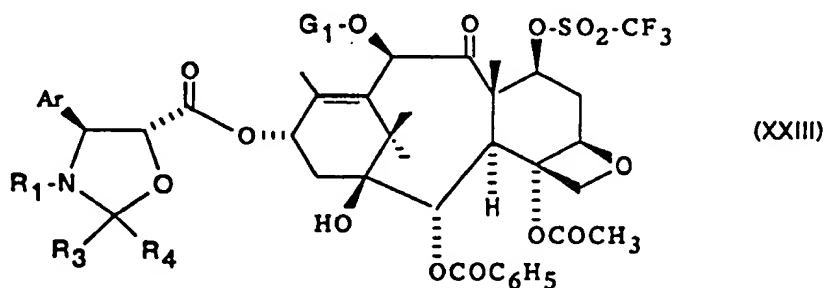
III protected in position 7, preferably with a silylated radical, with an alkoxy acetic acid halide or with an alkyl halide.

Generally, the reaction of a
5 trifluoromethanesulphonic acid derivative is carried out in an inert organic solvent (optionally halogenated aliphatic hydrocarbons, or aromatic hydrocarbons) in the presence of an organic base such as an aliphatic tertiary amine (triethylamine) or pyridine, at a
10 temperature of between -50 and +20°C.

Generally, the introduction of an alkoxyacetyl group is carried out by treating the protected 10-deacetylbaecatin III with an alkoxyacetic acid halide, the procedure being carried out in a basic
15 organic solvent such as pyridine at a temperature close to 20°C.

Generally, the introduction of an alkyl radical is carried out by treating the 10-deacetylbaecatin III, protected and metallized in
20 position 10, by means, for example, of an alkali metal hydride (sodium hydride) or a metallic alkylide (butyllithium), with an alkyl halide.

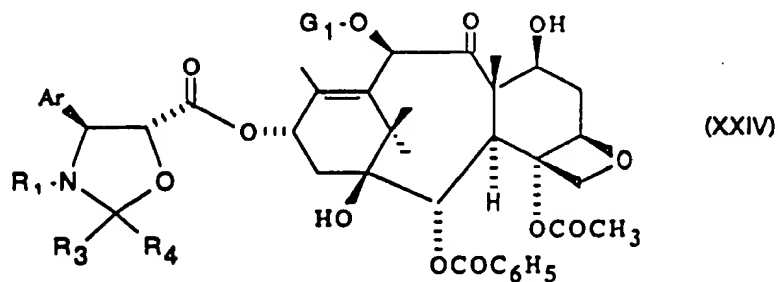
2) by the action of an alkali metal halide (sodium iodide or potassium fluoride) or an alkali metal azide
25 (sodium azide) or a quaternary ammonium salt or an alkali metal phosphate on a product of general formula:



in which Ar, R₁, R₃, R₄ and G₁ are defined as above.

Generally, the reaction is carried out in an organic solvent chosen from ethers (tetrahydrofuran, diisopropyl ether or methyl t-butyl ether) and nitriles (acetonitrile), alone or in the form of a mixture, at a temperature of between 20°C and the boiling temperature of the reaction mixture.

The product of general formula (XXIII) can be obtained by the action of a trifluoromethanesulphonic acid derivative such as the anhydride or N-phenyltrifluoromethanesulphonimide on a taxoid of general formula:

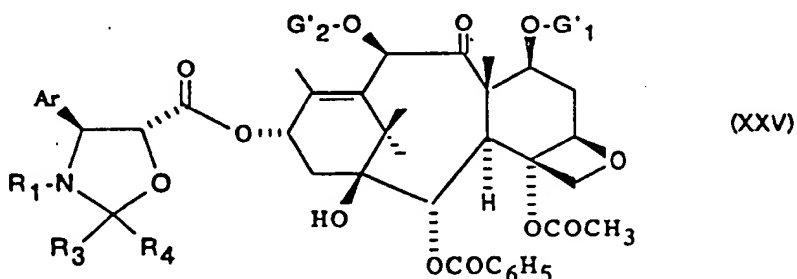


in which Ar, R₁, R₃, R₄ and G₁ are defined as above.

Generally, the reaction is carried out in an inert organic solvent (optionally halogenated aliphatic hydrocarbons, or aromatic hydrocarbons) in the presence

of an organic base such as an aliphatic tertiary amine (triethylamine) or pyridine, at a temperature of between -50 and +20°C.

The taxoid of general formula (XXIV), in which G_1 represents a hydrogen atom or an acetyl radical, can be obtained from a product of general formula:



in which Ar, R_1 , R_3 and R_4 are defined as above, G'_1 represents a hydroxy-protecting group and G'_2 represents an acetyl, alkoxyacetyl or alkyl radical or a hydroxy-protecting group, by replacement of the protecting groups G'_1 and optionally G'_2 by hydrogen atoms.

The radicals G'_1 and G'_2 , when they represent a hydroxy-protecting group, are preferably 2,2,2-trichloroethoxycarbonyl or 2-(2-trichloromethylpropoxy)carbonyl radicals or trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl or triarylsilyl radicals in which the alkyl portions contain 1 to 4 carbon atoms and the aryl portions are preferably phenyl radicals, it being possible, in addition, for G'_2 to represent an alkoxyacetyl radical.

When G'_1 and G'_2 represent a 2,2,2-trichloroethoxycarbonyl or 2-(2-trichloromethylpropoxy)carbonyl radical, the replacement of the protecting groups by hydrogen atoms is carried out using zinc, optionally combined with copper, in the presence of acetic acid at a temperature of between 20 and 60°C or by means of an inorganic or organic acid such as hydrochloric acid or acetic acid in solution in an aliphatic alcohol containing 1 to 3 carbon atoms or an aliphatic ester such as ethyl acetate, isopropyl acetate or n-butyl acetate in the presence of zinc optionally combined with copper.

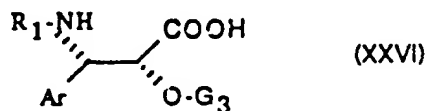
When G'_1 represents a silylated radical and G'_2 represents an acetyl, alkoxyacetyl or alkyl radical, the replacement of the protecting group G'_1 by a hydrogen atom can be carried out by means of, for example, gaseous hydrochloric acid in ethanolic solution at a temperature close to 0°C, under conditions which are without effect on the rest of the molecule.

When G'_2 represents an alkoxyacetyl radical, its optional replacement by a hydrogen atom is carried out by treatment in alkaline medium or by the action of a zinc halide under conditions which do not affect the rest of the molecule. Generally, the alkaline treatment is carried out by the action of ammonia in aqueous-alcoholic medium, at a temperature close to 20°C. Generally, the treatment with a zinc halide, preferably

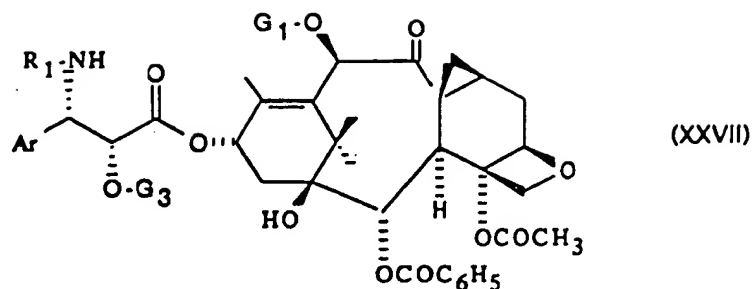
zinc iodide, is carried out in methanol at a temperature close to 20°C.

The product of general formula (XXV) can be obtained under the conditions described in international application PCT/WO 9209589.

The new derivatives of general formula (I) can also be obtained by esterification of a product of general formula (VI) by means of an acid of general formula:



in which Ar and R₁ are defined as above and G₃ represents a hydroxy-protecting group chosen from methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, (β-trimethylsilyloxy)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxymethyl, 2,2,2-trichloroethoxycarbonyl or 2-(2-trichloromethylpropoxy)carbonyl radicals or CH₂-Ph radicals in which Ph represents a phenyl radical optionally substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms, or an activated derivative of this acid, to give a product of general formula:



in which Ar, R_1 , G_1 , G_2 and G_3 are defined as above, followed by the replacement of the protecting groups G_1 , G_2 and G_3 by hydrogen atoms to give a product of general formula (I).

5 The esterification can be performed under the conditions described above for the esterification of the product of general formula (VI) by means of an acid of general formula (VII).

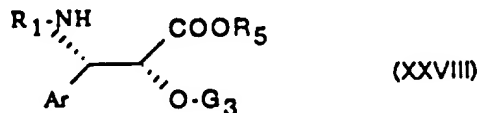
10 The replacement of the protecting groups G_1 and G_3 of the product of general formula (XXVII) by a hydrogen atom is carried out by treatment with zinc, optionally combined with copper, in the presence of acetic acid at a temperature of between 30 and 60°C or by means of an inorganic or organic acid such as

15 hydrochloric acid or acetic acid in solution in an aliphatic alcohol containing 1 to 3 carbon atoms or an aliphatic ester such as ethyl acetate, isopropyl acetate or n-butyl acetate in the presence of zinc optionally combined with copper, when G_1 and G_3

20 represent a 2,2,2-trichloroethoxycarbonyl or 2-(2-trichloromethylpropoxy)carbonyl radical. The replacement of the protecting group G_2 , when it

represents a silylated radical or an acetal residue,
 can be carried out by treatment in acidic medium such
 as for example hydrochloric acid in solution in an
 aliphatic alcohol containing 1 to 3 carbon atoms
 5 (methanol, ethanol, propanol or isopropanol) or aqueous
 hydrofluoric acid at a temperature of between 0 and
 40°C, when it represents an acetal residue, the
 replacement of the protecting group G_1 then being
 carried out under the conditions described above. When
 10 G_3 represents a group $-CH_2-Ph$, the replacement of this
 protecting group with a hydrogen atom can be carried
 out by hydrogenolysis in the presence of a catalyst.

The acid of general formula (XXVI) can be
 obtained by saponification of an ester of general
 15 formula:



in which Ar, R_1 , R_5 and G_3 are defined as above.

Generally, the saponification is carried out
 by means of an inorganic base (alkali metal hydroxide,
 carbonate or bicarbonate) in aqueous-alcoholic medium
 20 (methanol-water) at a temperature of between 10 and
 40°C.

The ester of general formula (XXVIII) can be
 obtained according to the usual methods for the
 preparation of ethers, and more particularly according
 25 to the procedures described by J-N. DENIS et al.,

J. Org. Chem., 51, 46-50 (1986), from a product of general formula (XI).

The new products of general formula (I) obtained using the procedures according to the invention can be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) have remarkable biological properties.

In vitro, measurement of the biological activity is carried out on tubulin extracted from pig brain by the method of M.L. Shelanski et al. Proc. Natl. Acad. Sci. USA, 70, 765-768 (1973). The study of the depolymerization of the microtubules into tubulin is carried out according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, série II, 501-503 (1981). In this study, the products of general formula (I) proved at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) proved active in mice grafted with the B16 melanoma at doses of between 1 and 10 mg/kg intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties and more particularly an activity on tumours which are resistant to Taxol® or Taxotere®. Such tumours comprise colon tumours which have a high expression of the *mdr* 1 gene (multi-drug resistance gene). Multi-drug resistance is a common term relating to the resistance of a tumour to various products of differing structures

and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

5 In particular, it has been found that the new products of the present invention which comprise the products of Examples 1, and 3 have a better multi-drug resistance than that of Taxol[®] and Taxotere[®]. Furthermore, it has been found, surprisingly, that the
10 product of Example 3 has better multi-drug resistance properties than that of the products of Examples 1 and 2.

The following examples illustrate the present invention.

15 EXAMPLE 1

A solution of 2.01 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-
20 oxazolidinecarboxylate in 20 cm³ of formic acid is stirred for 4 hours at a temperature close to 20°C and then concentrated to dryness under reduced pressure (0.27 kPa) at 40°C. The foam obtained is dissolved in 100 cm³ of dichloromethane and the solution obtained is
25 supplemented with 20 cm³ of a saturated aqueous sodium hydrogen carbonate solution. The aqueous phase is separated after settling has taken place and extracted

with 20 cm³ of dichloromethane. The organic phases are pooled, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 1.95 g of a white foam are obtained
5 which are purified by chromatography on 200 g of silica (0.063-0.2 mm) contained in a column 7 cm in diameter, eluting with a dichloromethane-methanol mixture (98-2 by volume) and collecting 30 cm³ fractions. The fractions containing only the desired product are
10 pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 1.57 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-amino-2-hydroxy-3-phenylpropionate are obtained in the
15 form of a white foam.

To a solution of 400 mg of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-amino-2-hydroxy-3-phenylpropionate in 1 cm³ of
20 dichloromethane, kept under an argon atmosphere, are added 60 mg of sodium hydrogen carbonate and then, dropwise, at a temperature close to 20°C, a solution of 0.16 g of di-tert-butyl dicarbonate in 1 cm³ of dichloromethane. The solution obtained is stirred for
25 64 hours at a temperature close to 20°C and then supplemented with a mixture of 5 cm³ of distilled water and 10 cm³ of dichloromethane. The organic phase is washed with three times 2 cm³ of distilled water. The

organic phase is dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 317 mg of a white foam are thus obtained which are purified by chromatography on

5 30 g of silica (0.063-0.2 mm) contained in a column 3 cm in diameter, eluting with a dichloromethane-methanol mixture (95-5 by volume) and collecting 5 cm³ fractions. The fractions containing only the desired product are pooled and concentrated to dryness under

10 reduced pressure (0.27 kPa) at 40°C for 2 hours. 161 mg of 4-isotoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate are thus obtained in the form of a

15 white foam whose characteristics are the following:

- specific rotation: $[\alpha]_D^{20} = -17^\circ$ (c = 0.482; methanol)
- proton NMR spectrum: (400 MHz; CDCl₃; temperature of 323 K; δ in ppm; coupling constants J in Hz): 1.21 (s, 3H: -CH₃, 16 or 17); 1.28 (s, 3H: -CH₃, 16 or 17); 1.34 [s, 9H: -C(CH₃)₃]; from 1.30 to 1.50 (mt, 1H: -H₇); 1.80 and
- 20 2.36 (2mt, 1H each: -CH₂- of cyclopropane); 1.88 (s, 3H: -CH₃, 18); 2.13 [mt, 1H: -(CH)-H₆]; 2.26 [dd, 1H, J = 15 to 8.5: -(CH)-H₁₄]; 2.35 (s, 3H: -COCH₃); from 2.35 to 2.50 [mt, 2H: -(CH) -H₁₄ and -(CH)-H₆]; 3.21
- 25 (d, 1H, J = 4: -OH 2'); 4.08 [d, 1H, J = 8: -(CH)-H₂₀]; 4.16 (d, 1H, J = 7: -H₃); 4.18 (s, 1H, -OH 10); 4.31 [d, 1H, J = 8: -(CH)-H₂₀]; 4.61 (dd, 1H, J = 4 and 2: -H_{2'}); 4.74 (d, 1H, J = 4: -H₅); 5.00 (s, 1H: -H₁₀); 5.26

(dd, 1H, $J = 9$ and 2:-H 3'); 5.33 (d, 1H, $J = 9$:-NH 3'); 5.69 (d, 1H, $J = 7$:-H 2); 6.29 (d, 1H, $J = 8.5$:-H 13); from 7.30 to 7.50 [mt, 5H:-C₆H₅ in 3' (-H 2 to -H 6); 7.51 [t, 2H, $J = 7.5$:-OCOC₆H₅ (-H 3 and H 5)]; 7.60
 5 [t, 1H, $J = 7.5$:-OCOC₆H₅ (-H 4)]; 8.14 [d, 2H, $J = 7.5$:-OCOC₆H₅ (-H 2 and H 6)].

The 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-
 10 phenyl-5-oxazolidinecarboxylate can be prepared in the following manner:

To a solution of 2.5 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-9-oxo-7 β -trifluoromethanesulphonate-11-taxen-13 α -yl (4S,5R)-3-
 15 tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate in 25 cm³ of anhydrous acetonitrile and 3 cm³ of anhydrous tetrahydrofuran, kept under an argon atmosphere, are added 2.5 g of sodium azide. The reaction mixture is heated for
 20 2 hours, with stirring and under an argon atmosphere at a temperature close to 80°C, then cooled to a temperature close to 20°C and supplemented with 30 cm³ of distilled water. The aqueous phase is separated by decantation and then extracted with 20 cm³ of
 25 dichloromethane. The combined organic phases are dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 2.44 g of a yellow foam are thus obtained which are

purified by chromatography on 300 g of silica (0.063-0.2 mm) contained in a column 8 cm in diameter, eluting with a dichloromethane-ethyl acetate mixture (90-10 by volume) and collecting 60 cm³ fractions.

5 Fractions 47 to 70 are pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 2.01 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-
10 phenyl-5-oxazolidinecarboxylate are thus obtained in the form of a white foam.

The 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-9-oxo-7 β -trifluoromethanesulphonate-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-
15 dimethyl-4-phenyl-5-oxazolidinecarboxylate can be prepared in the following manner:

To a solution of 2.86 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,7 β ,10 β -trihydroxy-9-oxo-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-
20 dimethyl-4-phenyl-5-oxazolidinecarboxylate in 29 cm³ of anhydrous dichloromethane, kept under an argon atmosphere, are added 0.955 cm³ of pyridine and 50 mg of powdered activated 4Å molecular sieve. The reaction mixture is cooled to a temperature close to -35°C,
25 slowly supplemented with 0.85 cm³ of trifluoromethanesulphonic anhydride, stirred at a temperature close to -5°C for 15 minutes and supplemented with 10 cm³ of distilled water. After filtration on sintered glass

provided with celite and rinsing off the sintered glass with 3 times 10 cm³ of a methanol-dichloromethane mixture (10-90 by volume), the aqueous phase is separated after settling has taken place and extracted with twice 10 cm³ of dichloromethane. The organic phases are pooled, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 3.87 g of a white foam are obtained which are purified by chromatography on 400 g of silica (0.063-0.2 mm) contained in a column 10 cm in diameter, eluting with a dichloromethane-ethyl acetate gradient (from 97.5-2.5 to 90-10 by volume) and collecting 80 cm³ fractions. The fractions containing only the desired product are pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 3.0 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-9-oxo-7 β -trifluoromethanesulphonate-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate are thus obtained in the form of a white foam.

The 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,7 β ,10 β -trihydroxy-9-oxo-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate can be prepared in the following manner:

A solution of 24.35 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-9-oxo-7 β ,10 β -[bis(2,2,2-trichloroethoxy)carbonyloxy]-1 β -hydroxy-11-taxen-13 α -yl

(4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate in a mixture of 130 cm³ of ethyl acetate and 46.5 cm³ of acetic acid is heated, with stirring and under an argon atmosphere up to a temperature close to 60°C and then supplemented with 40 g of zinc powder. The reaction mixture is then stirred for 30 minutes at 60°C and then cooled to a temperature close to 20°C and filtered on sintered glass provided with celite. The sintered glass is washed with 100 cm³ of a methanol-dichloromethane mixture (20-80 by volume); the filtrates are pooled and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature close to 40°C.

The residue is supplemented with 500 cm³ of dichloromethane. The organic phase is washed with twice 50 cm³ of a saturated aqueous sodium hydrogen carbonate solution and then with 50 cm³ of distilled water. The aqueous phases obtained after settling has taken place and pooled are extracted with twice 30 cm³ of dichloromethane. The organic phases are pooled, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 19.7 g of a white foam are obtained which are purified by chromatography on 800 g of silica (0.063-0.2 mm) contained in a column 10 cm in diameter, eluting with a dichloromethane-methanol gradient (from 100-0 to 97-3 by volume) and collecting 80 cm³ fractions. The fractions containing only the desired product are

pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 16.53 g of 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,7 β ,10 β -trihydroxy-9-oxo-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate in the form of a white foam.

The 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-9-oxo-7 β ,10 β -[bis(2,2,2-trichloroethoxy)carbonyloxy]-1 β -hydroxy-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate can be prepared according to the method described in international application PCT WO 9209589.

EXAMPLE 2

To a solution of 550 mg of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-amino-2-hydroxy-3-phenylpropionate are added 45 cm³ of distilled water, 45 cm³ of a saturated aqueous sodium hydrogen carbonate solution and then, dropwise, at a temperature close to 20°C, 0.096 cm³ of benzoyl chloride. The mixture obtained is stirred for 10 minutes at a temperature close to 20°C. After settling has taken place, the aqueous phase is extracted with twice 30 cm³ of ethyl acetate. The combined organic phases are dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 670 mg of a white foam are thus obtained which are

purified by chromatography at atmospheric pressure on
 50 g of silica (0.063-0.2 mm) contained in a column
 2.5 cm in diameter, eluting with a methanol-
 dichloromethane mixture (1-99 then 2.5-97.5 by volume)
 5 and collecting 10 cm³ fractions. The fractions
 containing only the desired product are pooled and
 concentrated to dryness under reduced pressure
 (2.7 kPa) at 40°C. 610 mg of a white foam are thus
 obtained. A sample of 300 mg is purified by preparative
 10 chromatography on 12 thin-layer silica plates
 (Kieselgel 60F254, Merck; thickness 0.25 mm), eluting
 with a methanol-dichloromethane mixture (3-97 by
 volume). After elution of the zone corresponding to the
 main product with a methanol-dichloromethane mixture
 15 (10-90 by volume) and then evaporation of the solvents
 under reduced pressure (0.27 kPa) at a temperature
 close to 40°C, 155.2 mg of 4 α ,10 β -diacetoxy-2 α -
 benzyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-
 oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-benzoylamino-2-
 20 hydroxy-3-phenylpropionate are obtained in the form of
 a white foam whose characteristics are the following:
 - specific rotation: $[\alpha]_D^{20} = -30.5^\circ$ (c = 0.491;
 methanol)
 - proton NMR spectrum: (300 MHz; CDCl₃; δ in ppm;
 25 coupling constants J in Hz): 1.27 (s, 3H: -CH₃, 16 or
 17); 1.30 (s, 3H: -CH₃, 16 or 17); 1.40 (mt, 1H: -H7);
 1.62 and 2.25 (q and m, 1H each: CH₂ of cyclopropane);
 1.85 (s, 3H: -CH₃, 18); 1.96 (s, 1H: -OH in 1); 2.05 and

2.48 (d and m, 1H each: $-\text{CH}_2-$ in 6); 2.24 (s, 3H: $-\text{COCH}_3$ in 10); 2.28 and 2.50 (m, 1H each: $-\text{CH}_2$ in 14); 2.45 (s, 3H: $-\text{COCH}_3$ in 4); 3.52 (d, 1H: $-\text{OH}$ in 2'); 4.10 and 4.35 (d, 1H each: $-\text{CH}_2-$ in 20); 4.11 (d, 1H: $-\text{H}_3$); 4.77 (broad d, 1H: $-\text{H}_5$); 4.82 (dd, 1H: $-\text{H}_2'$); 5.70 (d, 1H: $-\text{H}$ in 2); 5.84 (dd, 1H: $-\text{H}_3'$); 6.30 (broad t, 1H: $-\text{H}_{13}$); 6.36 (s, 1H: $-\text{H}_{10}$); 7.00 (d, 1H: $-\text{CONH}-$); from 7.35 to 8.30 (m, 15H: $-\text{C}_6\text{H}_5$ in 3', $-\text{OCOC}_6\text{H}_5$ and NHCOC_6H_5).

10 The $4\alpha,10\beta$ -diacetox-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R, 3S)-3-amino-2-hydroxy-3-phenylpropionate can be prepared by carrying out the procedure under the conditions described in Example 1 for the preparation
15 of 4-acetox-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-amino-2-hydroxy-3-phenylpropionate. Thus, starting with 1.6 g of $4\alpha,10\beta$ -diacetox-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidincarboxylate, 1.14 g of
20 $4\alpha,10\beta$ -diacetox-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl are obtained in the form of a white foam.

25 The $4\alpha,10\beta$ -diacetox-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidincarboxylate can be under the

conditions described in Example 1 for the preparation of 4 α -acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate. Thus, starting with 2.2 g of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-9-oxo-7 β -trifluoromethanesulphonate-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate, 1.62 g of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate are obtained in the form of a white foam.

The 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-9-oxo-7 β -trifluoromethanesulphonate-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate can be under the conditions described in Example 1 for the preparation of 4 α -acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,10 β -dihydroxy-9-oxo-7 β -trifluoromethanesulphonate-19-nor-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate. Thus, starting with 2.4 g of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,7 β -dihydroxy-9-oxo-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate, 2.46 g of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-9-oxo-7 β -

trifluoromethanesulphonate-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidincarboxylate are obtained in the form of a white foam.

- 5 The 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,7 β -dihydroxy-9-oxo-11-taxen-13 α -yl (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidincarboxylate can be prepared under the conditions described in International Application
- 10 PCT WO 9209589.

EXAMPLE 3

- To a solution of 550 mg of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-amino-2-hydroxy-3-phenylpropionate in 1 cm³ of dichloromethane, kept
- 15 under an argon atmosphere, are added 76 mg of sodium hydrogen carbonate and then, dropwise, at a temperature close to 20°C, a solution of 197 mg of di-tert-butyl dicarbonate in 1 cm³ of dichloromethane. The solution
- 20 obtained is stirred for 15 hours at a temperature close to 20°C and then supplemented with a mixture of 5 cm³ of distilled water and 10 cm³ of dichloromethane. The aqueous phase is extracted with 5 cm³ of dichloromethane. The combined organic phases are dried
- 25 over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 780 mg of a white foam are thus obtained which are purified by chromatography at atmospheric pressure on

50 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol-dichloromethane mixture (1-99 then 2.5-97.5 by volume) and collecting 10 cm³ fractions. The fractions

5 containing only the desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 660 mg of a white foam are thus obtained. A sample of 300 mg is purified by preparative chromatography on 12 thin-layer silica plates

10 (Kieselgel 60F254, Merck; thickness 0.25 mm), eluting with a methanol-dichloromethane mixture (4-96 by volume). After elution of the zone corresponding to the main product with a methanol-dichloromethane mixture (10-90 by volume) and then evaporation of the solvents

15 under reduced pressure (0.27 kPa) at a temperature close to 40°C, 159.7 mg of 4 α ,10 β -diacetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β -hydroxy-7 β ,8 β -methylene-9-oxo-19-nor-11-taxen-13 α -yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate are

20 obtained in the form of a white foam whose characteristics are the following:

- specific rotation: $[\alpha]_D^{20} = -34^\circ$ (c = 0.564; methanol)
- proton NMR spectrum: (400 MHz; CDCl₃; δ in ppm; coupling constants J in Hz): 1.28 (s, 3H: -CH₃, 16 or 17); 1.30 (s, 9H: -C(CH₃)₃); 1.38 (mt, 1H: -H7); 1.60 (s, 3H: -CH₃, 16 or 17); 1.68 and 2.25 (t and m, 1H each; CH₂- of cyclopropane); 1.85 (s, 3H: -CH₃, 18); 2.10 and 2.45 (d and td, 1H each: -CH₂- in 6); 2.23 (s, 3H:

-COCH₃ in 10); 2.22 and 2.40 (m, 1H each: -CH₂- in 14);
 2.40 (s, 3H: -COCH₃ in 4); 3.28 (d, 1H: -OH in 2');
 4.05 and 4.22 (d, 1H each: -CH₂- in 20); 4.10 (d, 1H:
 -H₃); 4.62 (broad s, 1H: -H₂'); 4.73 (d, 1H: -H₅); 5.29
 5 (broad d, 1H: -H₃'); 5.37 (d, 1H: -CONH-); 5.67 (d, 1H:
 -H in 2); 6.28 (broad t, 1H: -H₁₃); 6.33 (s, 1H: -H₁₀);
 from 7.30 to 7.45 (mt, 5H: -C₆H₅ in 3'); 7.51 [t, 2H:
 -OCOC₆H₅ (-H₃ and -H₅)]; 7.61 [t, 1H: -OCOC₆H₅ (-H₄)];
 8.17 [d, 2H: -OCOC₆H₅ (-H₂ and -H₆)].

10 EXAMPLE 4

To a solution of 100 mg of
 10-deacetylbaecatin III in a mixture of 3 cm³ of
 tetrahydrofuran and 0.05 cm³ of pyridine cooled to a
 temperature close to -78°C and kept under an argon
 15 atmosphere, is added, dropwise, 0.09 cm³ of trifluoro-
 methanesulphonic anhydride. The temperature is allowed
 to rise slowly to a temperature close to 0°C over
 approximately one hour, then up to a temperature close
 to 20°C over approximately one hour. After 2 hours at a
 20 temperature close to 20°C, 200 mg of tetrabutyl-
 ammonium iodide are added, then the solution is heated
 at the boiling temperature of the solvent for 15 hours.
 After cooling to a temperature close to 20°C, 10 cm³ of
 ethyl acetate and then 1 cm³ of distilled water are
 25 added. After separation after settling has taken place,
 the organic phase is dried over magnesium sulphate,
 filtered and concentrated to dryness under reduced
 pressure (2.7 kPa) at 40°C. 116 mg of a yellow oil are

thus obtained which are purified by chromatography at atmospheric pressure on 30 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter, eluting with an ethyl acetate-dichloromethane mixture, with an
 5 elution gradient from 0-100 to 80-20 by volume. The fractions containing the desired product are pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C. 10.3 mg of 10-deacetyl-7 β ,8 β -methylene-19-norbaccatin III are thus obtained in the
 10 form of a white foam whose characteristics are the following:

- proton NMR spectrum: (400 MHz; CDCl₃; δ in ppm; coupling constants J in Hz): 1.14 (s, 3H: -CH₃ in 16 or 17); 1.42 (mt, 1H: -H in 7); 1.76 and 2.31 (t and m, 1H
 15 each; CH₂ of cyclopropane); 2.07 (s, 3H: -CH₃ in 18); 2.15 and 2.50 (broad d and td, 1H each: CH₂- in 6); 2.30 (s, 3H: -COCH₃ in 4); 2.28 and 2.35 (m, 1H each: -CH₂ in 14); 4.11 and 4.37 (d, 1H each: -CH₂ in 20);
 4.28 (d, 1H: -H₃ in 3); 4.79 (d, 1H: -H in 5); 4.88
 20 (broad t, 1H: -H in 13); 5.09 (s, 1H: -H in 10); 5.66 (d, 1H: -H in 2); 7.51 [t, 2H: -OCOC₆H₅ (-H in 3 and 5)]; 7.61 [t, 1H: -OCOC₆H₅ (-H in 4)]; 8.17 [d, 2H: -OCOC₆H₅ (-H in 2 and 6)].

¹³C NMR spectrum: (100 MHz; CDCl₃; δ in ppm; uncoupled;
 25 s = singlet, d = doublet; t = triplet; q = quadruplet): 15 (q, C18); 16.5 (t, C19); 20 and 27 (q, C16 and C17); 22.5 (q, -COCH₃); 26.5 (t, C6); 33 (d, C7); 35 (s, C8); 39 (d, C3); 39.5 (t, C14); 43 (s, C15); 68 (d, C13); 76

(t, C20); 76.2 (d, C10); 79.5 (s, C1); 80 (s, C4); 81 (d, C2); 85 (d, C5); 129 (d, C2: -OCOC₆H₅); 130 (s, C1 of -OCOC₆H₅); 130.5 (d, C3 of -OCOC₆H₅); 134 (d, C4 of -OCOC₆H₅); 136 (s, C11); 143 (s, C12); 168 (s, 5 -OCOC₆H₅); 171 (s, -COCH₃); 210 (s, C9).

The new products of general formula (I) manifest a significant inhibitory activity with respect to abnormal cell proliferation and possess therapeutic properties which permit the treatment of patients 10 having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or nonmalignant cells of various tissues and/or organs, comprising, with no limitation being implied, muscle, 15 bone or connective tissues, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive tract, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, 20 cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangioma, chorioma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanomas, multiple myelomas, lymphatic leukaemias and acute or chronic granulocytic 25 lymphomas. The new products according to the invention are particularly useful for the treatment of cancer of the ovary. The products according to the invention can be used to prevent or retard the appearance or

reappearance of the pathological conditions or to treat these pathological conditions.

The products according to the invention can be administered to a patient in various forms adapted to the chosen route of administration which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administrations. Intraperitoneal or intravenous administration is more particularly preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I) in a sufficient quantity adapted to use in human or veterinary therapy. The compositions can be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants, carriers or excipients. Suitable carriers include diluents, sterile aqueous media and various nontoxic solvents. Preferably, the compositions are provided in the form of aqueous solutions or suspensions, of injectable solutions which may contain emulsifying agents, colorants, preservatives or stabilizers.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, aqueous or

nonaqueous sterile solutions or suspensions are used. For the preparation of nonaqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or paraffin oil or injectable organic esters
5 such as ethyl oleate can be used. The aqueous sterile solutions may consist of a solution of a pharmaceutically acceptable salt in solution in water. The aqueous solutions are suitable for intravenous administration in so far as the pH is appropriately
10 adjusted and isotonicity is achieved, for example, with a sufficient quantity of sodium chloride or glucose. The sterilization can be performed by heating or by any other means which does not adversely affect the composition.

15 It is clearly understood that all the products entering into the compositions according to the invention should be pure and nontoxic for the quantities used.

The compositions may contain at least 0.01 %
20 of therapeutically active product. The quantity of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared such that a single dose contains about 0.01 to 1000 mg of active product for parenteral
25 administration.

The therapeutic treatment can be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies,

immunotherapies or radiotherapies or biological response modifiers. The response modifiers include, with no limitation being implied, lymphokines and cytokines such as interleukins, interferons (α , β or δ) and TNF. Other chemotherapeutic agents which are useful in the treatment of disorders caused by abnormal proliferation of cells include, with no limitation being implied, alkylating agents like nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues like methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products like vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum like cisplatin, substituted ureas like hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone

acetate and megestrol acetate, oestrogens such as diethylstilbestrol and ethynylestradiol, antioestrogen such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

5 The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the form of administration, the particular product selected and the
10 characteristics specific to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders caused by abnormal cell proliferation. The products according to the invention can be administered
15 as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary,
20 increasingly higher doses will be administered until an optimum effect is obtained. For other patients, it may be necessary to administer maintenance doses 1 to 8 times per day, preferably 1 to 4 times according to the physiological needs of the patient considered. It is
25 also possible that for certain patients it may be necessary to use only one to two daily administrations.

In man, the doses are generally between 0.01 and 200 mg/kg. For intraperitoneal administration, the

doses will generally be between 0.1 and 100 mg/kg and, preferably, between 0.5 and 50 mg/kg and, still more specifically, between 1 and 10 mg/kg. For intravenous administration, the doses are generally between 0.1 and 50 mg/kg and, preferably, between 0.1 and 5 mg/kg and, still more specifically, between 1 and 2 mg/kg. It is understood that, in order to choose the most appropriate dosage, account should be taken of the route of administration, the patient's weight, his general state of health, his age and all factors which may influence the efficacy of the treatment.

The following example illustrates a composition according to the invention.

EXAMPLE

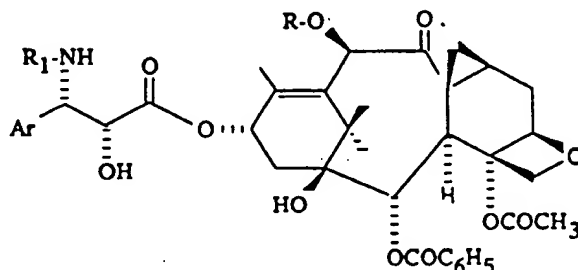
40 mg of the product obtained in Example 1 are dissolved in 1 cm³ of Emulphor EL 620 and 1 cm³ of ethanol and then the solution is diluted by addition of 18 cm³ of physiological saline.

The composition is administered by perfusion for 1 hour by introduction into physiological saline.

CLAIMS

[received by the International Office on 16 March 1994
(16.03.94); Claims 4-7, 33 and 34 added; Claims 4-28,
29 and 30 unchanged but renumbered 8-32, 35 and 36;
5 other claims unchanged (12 pages)]

1. New taxoids of general formula:



in which

R represents a hydrogen atom or an acetyl, alkoxyacetyl
or alkyl radical,

- 10 R₁ represents a benzoyl radical or a radical R₂-O-CO- in
which R₂ represents an alkyl, alkenyl, alkynyl,
cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or
heterocyclyl radical, and
Ar represents an aryl radical.

- 15 2. New derivatives according to claim 1 for
which:

R represents a hydrogen atom or an acetyl, alkoxyacetyl
or alkyl radical,

- 20 R₁ represents a benzoyl radical or a radical R₂-O-CO in
which R₂ represents:

- a straight or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted by one or more substituents, which are identical or different, chosen from halogen atoms and hydroxy radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals (optionally substituted at position 4 by an alkyl radical containing 1 to 4 carbon atoms or by a phenylalkyl radical whose alkyl portion contains 1 to 4 carbon atoms), cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, cyano radicals, carboxy radicals or alkoxycarbonyl radicals whose alkyl portion contains 1 to 4 carbon atoms,
 - or a phenyl radical optionally substituted by one or more radicals, which are identical or different, chosen from alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms,

- or a saturated or unsaturated 5- or

6-membered nitrogen-containing heterocyclyl radical optionally substituted by one or more alkyl radicals containing 1 to 4 carbon atoms, it being understood that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals may be optionally substituted by one or more alkyl radicals containing 1 to 4 carbon atoms, and

Ar represents a phenyl or a- or b-naphthyl radical optionally substituted by one or more atoms or radicals, chosen from halogen atoms (fluorine, chlorine, bromine, or iodine) and alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxy, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, it being understood that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or a- or b-naphthyl radicals or alternatively Ar represents a 5-membered aromatic heterocyclic radical containing one or more atoms, which are identical or different, chosen from nitrogen, oxygen or sulphur atoms, optionally substituted by one or more substituents, which are identical or different, chosen from halogen atoms

(fluorine, chlorine, bromine or iodine) and alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxy-carbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 to 10 carbon atoms, cyano radicals, carboxy radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms or alkoxy-carbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

20 3. New derivatives according to claim 1, for which R represents a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical, R_1 represents a benzoyl radical or a radical R_2 -O-CO- in which R_2 represents a t-butyl radical and Ar represents a phenyl radical.

25 4. New derivative according to claim 1, for which R represents an acetyl radical, R_1 represents a radical R_2 -O-CO- in which R_2 represents a t-butyl

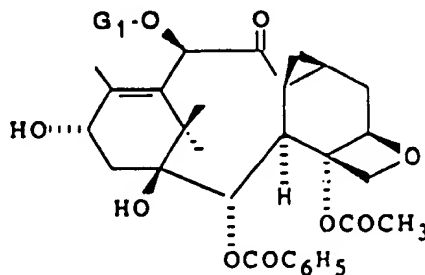
radical and Ar represents a phenyl radical.

5. New derivative according to claim 1, for which R represents an acetyl radical, R_1 represents a benzoyl radical and Ar represents a phenyl radical.

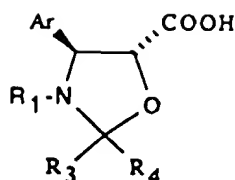
5 6. New derivative according to Claim 1, for which R represents a hydrogen atom, R_1 represents a radical R_2 -O-CO- in which R_2 represents a t-butyl radical and Ar represents a phenyl radical.

7. New derivative according to claim 1, for 10 which R represents a hydrogen atom, R_1 represents a benzoyl radical and Ar represents a phenyl radical.

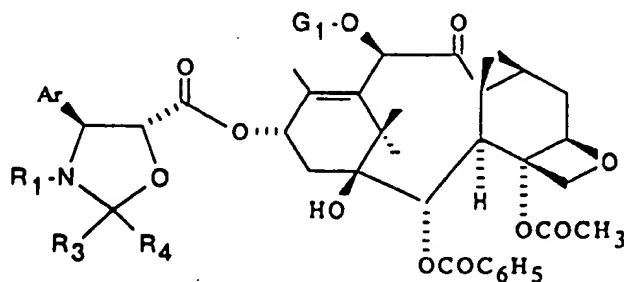
8. Process for the preparation of a product according to one of claims 1 to 7, characterized in that a product of general formula:



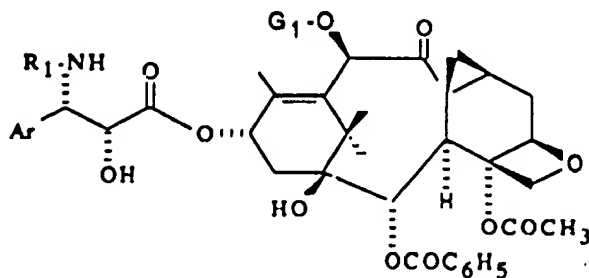
15 in which G_1 represents a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical or a hydroxy-protecting group, is esterified by means of an acid of general formula:



in which Ar and R₁ are defined as in one of claims 1 to 7, R₃ represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or an optionally substituted aryl radical and R₄ represents a hydrogen atom, to give a product of general formula:



in which Ar, R and R₁ are defined as in one of claims 1 to 7, R₃, R₄ and G₁ are defined as above, which is treated in acidic medium to give a product of general formula:



10 in which Ar, R₁ and G₁ are defined as above, and then the protecting group G₁ is optionally replaced by a

hydrogen atom and the product obtained is isolated.

9. Process according to claim 8,
characterized in that the esterification is carried out
by means of the free acid, the procedure being carried
5 out in the presence of a condensing agent chosen from
carbodiimides and reactive carbonates and an activating
agent chosen from aminopyridines in an organic solvent
chosen from ethers, ketones, esters, nitriles,
aliphatic hydrocarbons, halogenated aliphatic
10 hydrocarbons and aromatic hydrocarbons at a temperature
of between -10 and 90°C.

10. Process according to claim 8,
characterized in that the esterification by means of
the anhydride is carried out in the presence of an
15 activating agent chosen from aminopyridines in an
organic solvent chosen from ethers, esters, ketones,
nitriles, aliphatic hydrocarbons, halogenated aliphatic
hydrocarbons and aromatic hydrocarbons at a temperature
of between 0 and 90°C.

20 11. Process according to claim 8,
characterized in that the esterification is carried out
by means of a halide or an anhydride with an aliphatic
or aromatic acid, optionally prepared in situ, the
procedure being carried out in the presence of a base
25 chosen from tertiary aliphatic amines in an organic
solvent chosen from ethers, esters, ketones, nitriles,
aliphatic hydrocarbons, halogenated aliphatic

hydrocarbons and aromatic hydrocarbons at a temperature of between 0 and 80°C.

12. Process according to claim 8,
characterized in that the acid treatment is carried out
5 by means of an inorganic or organic acid in an organic solvent at a temperature of between -10 and 60°C.

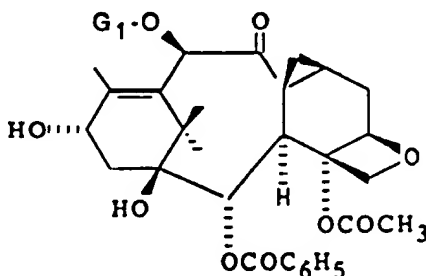
13. Process according to claim 12,
characterized in that the acid is chosen from
hydrochloric, sulphuric, acetic, methanesulphonic,
10 trifluoromethanesulphonic and p-toluenesulphonic acids, used alone or in the form of a mixture.

14. Process according to claim 12,
characterized in that the solvent is chosen from
alcohols, ethers, esters, halogenated aliphatic
15 hydrocarbons, aromatic hydrocarbons and nitriles.

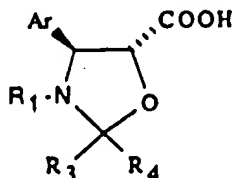
15. Process according to claim 8,
characterized in that the replacement by a hydrogen
atom of the protecting group G_1 , when it represents a
2.2,2-trichloroethoxycarbonyl or 2-(2-trichloromethyl-
20 propoxy)carbonyl radical, is carried out by treatment using zinc, optionally combined with copper, in the presence of acetic acid at a temperature of between 30 and 60°C or by means of an inorganic or organic acid such as hydrochloric acid or acetic acid in solution in
25 an aliphatic alcohol containing 1 to 3 carbon atoms or an aliphatic ester such as ethyl acetate, isopropyl acetate or n-butyl acetate in the presence of zinc

optionally combined with copper, and, when it represents an alkoxyacetyl radical, by treatment in alkaline medium by means of ammonia in aqueous-alcoholic medium at a temperature close to 20°C or by
 5 treatment using a zinc halide in methanol at a temperature close to 20°C.

16. Process for the preparation of a product according to one of claims 1 to 7, characterized in that a product of general formula:

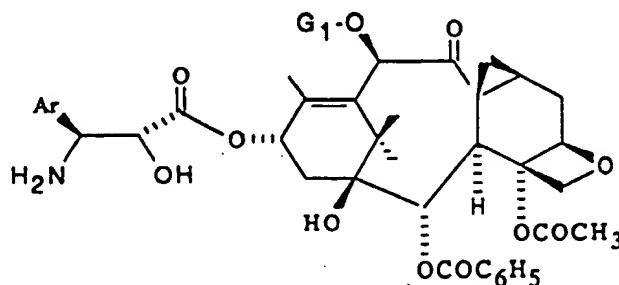


10 in which G_1 represents a hydrogen atom or an acetyl, alkoxyacetyl or alkyl radical or a hydroxy-protecting group, is esterified by means of an acid of general formula:

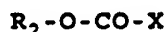


in which Ar and R_1 are defined as in one of claims 1 to
 15 7 and R_3 and R_4 , which are identical or different, represent an alkyl radical containing 1 to 4 carbon atoms or an aralkyl radical whose alkyl portion

contains 1 to 4 carbon atoms or an aryl radical, or alternatively R_3 represents a trihalomethyl radical or a phenyl radical substituted by a trihalomethyl radical and R_4 represents a hydrogen atom, or alternatively R_3 and R_4 form, together with the carbon atom to which they are attached, a 4- to 7-membered ring, to give, after treatment in acidic medium, a product of general formula:



in which Ar is defined as in one of claims 1 to 7 and G_1 is defined as above, which is acylated by means of benzoyl chloride or a reactive derivative of general formula:



in which R_2 is defined as in one of claims 1 to 7 and X represents a halogen atom or a residue $-O-R_2$ or $-O-CO-O-R_2$, and then the protecting group G_1 is replaced, if necessary, by a hydrogen atom, and the product obtained is isolated.

17. Process according to claim 16, characterized in that the esterification is carried out by means of the free acid, the procedure being carried

out in the presence of a condensing agent chosen from carbodiimides and reactive carbonates and an activating agent chosen from aminopyridines in an organic solvent chosen from ethers, ketones, esters, nitriles,
5 aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of between -10 and 90°C.

18. Process according to claim 16,
characterized in that the esterification by means of
10 the anhydride is carried out in the presence of an activating agent chosen from aminopyridines in an organic solvent chosen from ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature
15 of between 0 and 90°C.

19. Process according to claim 16,
characterized in that the esterification is carried out by means of a halide or an anhydride with an aliphatic or aromatic acid, optionally prepared in situ, the
20 procedure being carried out in the presence of a base chosen from tertiary aliphatic amines in an organic solvent chosen from ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature
25 of between 0 and 80°C.

20. Process according to claim 16,
characterized in that the acid treatment is carried out

by means of an inorganic or organic acid in an organic solvent at a temperature of between 0 and 50°C.

21. Process according to claim 20,
characterized in that the acid is chosen from
5 hydrochloric, sulphuric and formic acids.

22. Process according to claim 20,
characterized in that the solvent is chosen from
alcohols containing 1 to 3 carbon atoms.

23. Process according to claim 16,
10 characterized in that the acylation is carried out in
an inert organic solvent in the presence of an
inorganic or organic base.

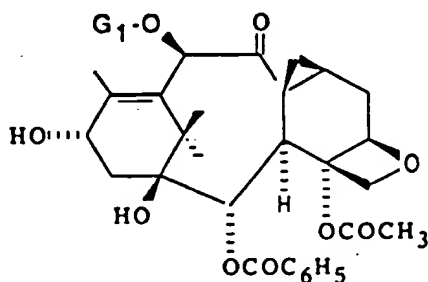
24. Process according to claim 23,
characterized in that the inert organic solvent is
15 chosen from esters and halogenated aliphatic
hydrocarbons.

25. Process according to one of claims 22,
23 or 24, characterized in that the procedure is
carried out at a temperature of between 0 and 50°C.

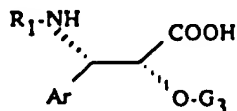
20 26. Process according to claim 16,
characterized in that the replacement by a hydrogen
atom of the protecting group G_1 , when it represents a
2,2,2-trichloroethoxycarbonyl or 2-(2-trichloromethyl-
propoxy)carbonyl radical, is carried out by treatment
25 using zinc, optionally combined with copper, in the
presence of acetic acid at a temperature of between 30
and 60°C or by means of an inorganic or organic acid

such as hydrochloric acid or acetic acid in solution in an aliphatic alcohol containing 1 to 3 carbon atoms or an aliphatic ester such as ethyl acetate, isopropyl acetate or n-butyl acetate in the presence of zinc optionally combined with copper, or, when it represents an alkoxy acetyl radical, by treatment in alkaline medium by means of ammonia in aqueous-alcoholic medium at a temperature close to 20°C or by treatment using a zinc halide in methanol at a temperature close to 20°C.

27. Process for the preparation of a product according to one of claims 1 to 7, characterized in that a product of general formula:

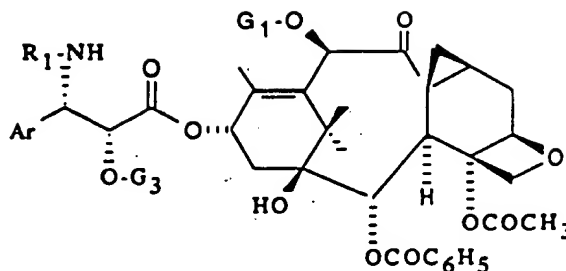


in which G_1 represents a hydrogen atom or an acetyl radical or a hydroxy-protecting group, is esterified by means of an acid of general formula:



in which Ar and R_1 are defined as in one of claims 1 to 7 and G_3 represents a hydroxy-protecting group, or of an activated derivative of this acid, to give a product

of general formula:



in which Ar, R₁, G₁ and G₃ are defined as above, whose protecting groups G₃ and optionally G₁ are replaced by a hydrogen atom, and the product obtained is isolated.

5 28. Process according to claim 27,
characterized in that the esterification is carried out
by means of the free acid, the procedure being carried
out in the presence of a condensing agent chosen from
carbodiimides and reactive carbonates and an activating
10 agent chosen from aminopyridines in an organic solvent
chosen from ethers, ketones, esters, nitriles,
aliphatic hydrocarbons, halogenated aliphatic
hydrocarbons and aromatic hydrocarbons at a temperature
of between -10 and 90°C.

15 29. Process according to claim 27,
characterized in that the esterification by means of
the anhydride is carried out in the presence of an
activating agent chosen from aminopyridines in an
organic solvent chosen from ethers, esters, ketones,
20 nitriles, aliphatic hydrocarbons, halogenated aliphatic
hydrocarbons and aromatic hydrocarbons at a temperature

of between 0 and 90°C.

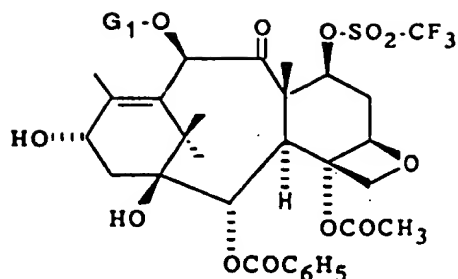
30. Process according to claim 27,
characterized in that the esterification is carried out
by means of a halide or an anhydride with an aliphatic
5 or aromatic acid, optionally prepared in situ, the
procedure being carried out in the presence of a base
chosen from tertiary aliphatic amines in an organic
solvent chosen from ethers, esters, ketones, nitriles,
aliphatic hydrocarbons, halogenated aliphatic
10 hydrocarbons and aromatic hydrocarbons at a temperature
of between 0 and 80°C.

31. Process according to claim 27,
characterized in that the replacement of the protecting
groups G_1 and G_3 by hydrogen atoms is carried out by
15 treatment with zinc, optionally combined with copper,
in the presence of acetic acid at a temperature of
between 30 and 60°C or by means of an inorganic or
organic acid such as hydrochloric acid or acetic acid
in solution in an aliphatic alcohol containing 1 to 3
20 carbon atoms or an aliphatic ester such as ethyl
acetate, isopropyl acetate or n-butyl acetate in the
presence of zinc optionally combined with copper, when
 G_1 and G_3 represent a 2,2,2-trichloroethoxycarbonyl or
2-(2-trichloromethylpropoxy)carbonyl radical, or by
25 treatment in acidic medium such as for example
hydrochloric acid in solution in an aliphatic alcohol
containing 1 to 3 carbon atoms (methanol, ethanol,

propanol or isopropanol) or aqueous hydrofluoric acid at a temperature of between 0 and 40°C when G₃ represents silylated radical or an acetal residue, followed by the replacement of the protecting group G₁ by treatment using zinc, optionally combined with copper, in the presence of acetic acid at a temperature of between 30 and 60°C or by means of an inorganic or organic acid such as hydrochloric acid or acetic acid in solution in an aliphatic alcohol containing 1 to 3 carbon atoms or an aliphatic ester such as ethyl acetate, isopropyl acetate or n-butyl acetate in the presence of zinc optionally combined with copper, or, when G₁ represents an alkoxyacetyl radical, by treatment in alkaline medium by means of ammonia in aqueous-alcoholic medium at a temperature close to 20°C or by treatment using a zinc halide in methanol at a temperature close to 20°C.

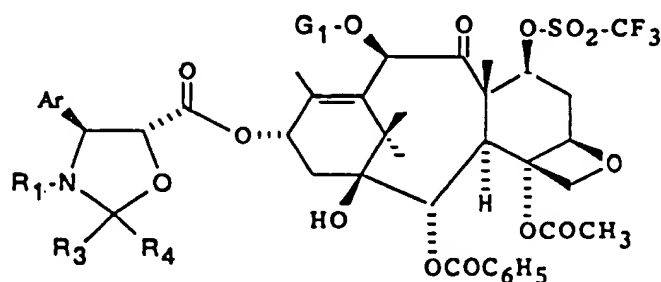
32. Process according to claim 27, characterized in that when G₃ represents a radical -CH₂-Ph, the replacement of the group by a hydrogen atom is carried out by hydrogenolysis, after replacing the protecting group G₁ under the conditions of claim 31.

33. New taxoid of general formula:



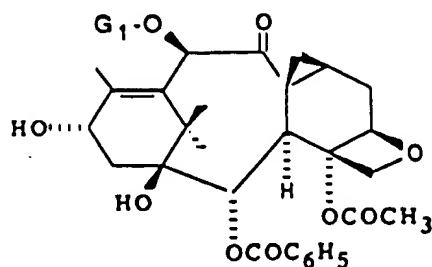
in which G_1 represents a hydrogen atom or an acetyl or alkoxyacetyl radical or a hydroxy-protecting group.

34. New taxoid of general formula:



in which G_1 represents a hydrogen atom or an acetyl or alkoxyacetyl radical or a hydroxy-protecting group, Ar and R_1 are defined as in one of claims 1 to 7 and R_3 and R_4 are defined as in one of claims 8 or 16.

35. New taxoid of general formula:



in which G_1 represents a hydrogen atom or an acetyl,

alkoxyacetyl or alkyl radical or a hydroxy-protecting group.

36. Pharmaceutical composition characterized in that it contains at least one product according to one of claims 1 to 7, in combination with one or more pharmaceutically acceptable products, whether inert or physiologically active.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 93/01201

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D305/14 A61K31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | JOURNAL OF MEDICINAL CHEMISTRY vol. 34, 1991, WASHINGTON US pages 992 - 998 F. GUERITTE-VOEGELEIN ET AL. 'RELATIONSHIP BETWEEN THE STRUCTURE OF TAXOL ANALOGUES AND THEIR ANTIMITOTIC ACTIVITY.' see page 992 - page 994 ----- | 1,30 |

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *B* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *A* document member of the same patent family

Date of the actual completion of the international search

22 February 1994

Date of mailing of the international search report

28. 02. 94

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Fax: (+31-70) 340-3016

Authorized officer

Francois, J

RAPPORT DE RECHERCHE INTERNATIONALE

Demr Internationale No

PCT/FR 93/01201

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 5 C07D305/14 A61K31/335

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)

CIB 5 C07D

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

| Catégorie * | Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents | no. des revendications visées |
|-------------|--|-------------------------------|
| A | JOURNAL OF MEDICINAL CHEMISTRY vol. 34, 1991, WASHINGTON US pages 992 - 998 F. GUERITTE-VOEGELEIN ET AL. 'RELATIONSHIP BETWEEN THE STRUCTURE OF TAXOL ANALOGUES AND THEIR ANTIMITOTIC ACTIVITY.' voir page 992 - page 994 ----- | 1,30 |

☐ Voir la suite du cadre C pour la fin de la liste des documents

☐ Les documents de familles de brevets sont indiqués en annexe

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- *Y* document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier
- *a* document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée

22 Février 1994

Date d'expédition du présent rapport de recherche internationale

28. 02. 94

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